Finally, we, like all those who work with PGI_2, are well aware of the weaknesses of plasma 6-keto-$PGF_{1\alpha}$ measurement as an index of PGI_2 generation. At the moment, however, no other method has been shown to be clearly superior to 6-keto-$PGF_{1\alpha}$ measurement in the study of PGI_2 production in vivo. Many recent papers of Dr Webster and his colleagues on PGI_2, as measured by plasma 6-keto-$PGF_{1\alpha}$ levels, tempt us to believe that he thinks in the same way.

OLAVI YLIKORKALA

University Department of Obstetrics and Gynaecology, Helsinki, Finland

LASSE VIINIKKA

University Department of Clinical Chemistry, Oulu, Finland

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Medical aspects of unemployment

SIR,—Professor I M Richardson's letter (16 January, p 193) rightly emphasises that a lot is already known about the medical effects of unemployment.

A study of community health, carried out in Glasgow in 1972, showed that unemployment not due to illness was a major predictor of the prevalence of mental and social symptoms, as well as being significantly associated with the presence of physical symptoms.[1] Quite apart from the personal and social consequences, the hidden costs of unemployment to the health service must be very large indeed. The medical profession may be unable to change the complex economic and social factors involved, but it can continue to draw attention to the health implications of the loss of employment for those who are fit to work.

There is, however, one area of unemployment where doctors do have a direct say and that is on medical unemployment. The evidence is now mounting that we are producing more qualified doctors than this country is able to employ. As the openings abroad are being closed owing to similar difficulties overseas, so the prospects for medical students become dimmer. Sooner or later it seems likely that the medical school intake in the United Kingdom will have to be reduced if we are not to be training doctors for the dole.

D R HANNAY

University Department of General Practice, Woodside Health Centre, Glasgow G20 7LR

1 Hannay DR. *The symptom iceberg: a study of community health.* London: Routledge and Kegan Paul, 1979.

Clinical science and medical art

SIR,—It saddens me that your reviewer Dr Brian Livesley (16 January, p 186) uses my book *Essentials of Clinical Diagnosis in Cardiology* to attack "the teaching of cardiology in general and postgraduate examinations in particular." Sour grapes from a geriatrician will not alter these and neither will facetious remarks about bats, butterflies, and angels. Dr Livesley should have no difficulty in finding compassion in his colleagues, be they teachers or examiners, but quite rightly observes that there is no space for it in a compendium of facts and information.

While one can understand his lack of enthusiasm for minutiae, your reviewer's disdain for eponyms is puzzling in view of his publicised interest in medical history. Surely eponyms provide one of the most effective ways of perpetuating the memory of members of our profession?

R S WINWOOD

Whipps Cross Hospital, London E11 1NR

Little new for audiologists

SIR,—As the series editor of "Studies in Developmental Paediatrics" (MTP Press), I would like to comment on Professor I G Taylor's review (2 January, p 41) entitled "Little new for audiologists" of volume 2 of the series, *The Development of Hearing: its Progress and Problems* by Sybil Yeates.

As is made quite clear both on the dust cover, in the series editor's note, and in Dr Yeates's own preface, these studies are designed for general practitioners, clinical medical officers, paediatricians, health visitors, and others concerned with developmental paediatrics. There has never been any intention of writing a textbook for audiologists. It seems therefore most unfair for Professor Taylor to state that "there is little new for audiologists" when the book is quite obviously not intended for them.

Dr Yeates is quite experienced and skilled enough to write such a book, had she a mind to do so; but that was not her brief. She was asked to write—and I quote from Professor Taylor's review—"to arouse interest in those otherwise unaware of the practice of clinical audiology," and to my mind she has admirably succeeded.

MARGARET POLLAK

Sir Wilfrid Sheldon Children's Centre, Belgrave Hospital for Children, London SW9 0JF

Cold in the jaw

SIR,—The Clinical Curio "Cold in the jaw" should have been called "Pain in the jaw from a cold wind." It can occur in several ways.[1] If the front teeth have lost enamel and dentine because of dental caries or a fracture the cold stimulus is more effective in stimulating the intradental nerves. This can cause pain which is not well localised, especially if several teeth are affected. It starts within a second or so of the application of the stimulus and lasts for a few seconds after the stimulus stops or until the teeth cool. Cold wind can also provoke an attack of idiopathic trigeminal neuralgia and patients occasionally say that they wear a scarf or (in one case) walk backwards into the wind.

A third way is that described in Dr I B Sneddon's note (14 November, p 1314). The cold wind cools the face. When the person returns to a warm room there is vasodilatation, which apparently involves the dental pulps as well, and the increase in blood pressure is sufficient to produce additional neural impulses along the dental nerves. This may feel only like a throbbing in the teeth concerned or may be painful. Such pain is not well localised and seems to spread in that part of the jaw. It passes off after intervals of a few minutes up to about half an hour. Such pain is made worse if disease is present, which may be generating neural impulses below the threshold of perception. This happened to me on a canal boating holiday when I went for a walk in a cold wind. Shortly after returning to the warm cabin pain developed in the right posterior part of my upper jaw. After it had passed off I repeated the walk with a scarf around my face but there was no pain on my returning to the warm cabin. Both tests were repeated with the same results. I also spent time walking in the wind with the scarf on but my mouth open (there was nobody about to see my stupid expression), but this did not provoke pain.

From these tests I decided that I might have a molar with dental caries sufficiently deep to be causing a mild pulpitis which was generating neural impulses below the threshold of perception; the reactive vasodilatation produced additional neural impulses and pain occurred by summation. It also seemed that the dental caries was well hidden from view and well protected from direct cold wind through my open mouth. My dentist found that this was the case and I needed pulp canal therapy. It follows that Dr Sneddon should see his dentist for a check-up—just in case.

J M MUMFORD

Department of Operative Dental Surgery, University of Liverpool School of Dental Surgery, Liverpool L69 3BX

1 Mumford JM. *Toothache and orofacial pain.* Edinburgh: Churchill Livingstone, 1976:118-21, 136-40, 310-4.

Paracetamol-induced acute renal failure in the absence of fulminant liver damage

SIR,—We were interested to see the report by Dr I Cobden and others (2 January, p 21), which confirms our observations that renal failure may complicate paracetamol overdosage in the absence of fulminant hepatic failure.[1 2] Over the period 1969-80 inclusive, 2060 unselected adult patients were admitted to the Edinburgh regional poisoning treatment centre after paracetamol overdosage and 33 (1·6%) developed renal failure, defined as an increase in plasma creatinine concentration to more than 250 μmol/l (2·82 mg/100 ml). Eighteen of these patients developed renal failure in the absence of hepatic failure or encephalopathy. The picture has changed somewhat since specific therapy for paracetamol poisoning was introduced in mid-1973 and renal failure is now virtually confined to severely poisoned patients admitted too late for effective treatment (table). We would take this matter even further than Dr Cobden and his colleagues and point out that renal failure may occasionally complicate paracetamol poisoning

Incidence of renal failure following paracetamol overdosage

Period	Total No of patients	At risk*	No (%) with renal failure
1969-mid-1973	360	57	7 (12·3%)
Mid-1973-1980	1700	267	26 (9·7%)
Mid-1973-1980: treated within 10 h		149	1 (0·7%)
Mid-1973-1980: too late for effective treatment		118	25 (21·2%)

*Plasma paracetamol concentration above a line joining semilogarithmic plots of 200 μg/ml at 4 h and 50 μg/ml at 12 h after ingestion.

in the absence of any clinical or biochemical evidence of liver damage, as shown by the following case reports.

The first patient was a 21-year-old man who was admitted three days after allegedly taking 15 g of paracetamol. Three days after admission the plasma creatinine peaked at 256 μmol/l (2·89 mg/100 ml) and the creatinine clearance was 38 ml/min. The second was a woman of 22 years who was admitted 12 hours after taking paracetamol and Veganin (containing aspirin 250 mg, paracetamol 250 mg, and codeine phosphate 9·58 mg per tablet). The plasma concentrations of paracetamol and salicylate were 50 and 125 μg/ml respectively and treatment with *N*-acetylcysteine was begun. The plasma creatinine concentration was 85 μmol/l (0·96 mg/100 ml) on admission but rose to 390 μmol/l (4·41 mg/100 ml) on the sixth day while the creatinine clearance fell to 10 ml/min. The third patient, a 23-year-old man, was admitted 11 hours after taking paracetamol in overdosage with a plasma concentration of 86 μg/ml. At the time D-penicillamine was being investigated as a possible antidote for paracetamol poisoning and he received 5 g intravenously over 20 hours. The plasma creatinine concentration rose to 450 μmol/l (5·0 mg/100 ml) on the fifth day. Serial liver function tests (including prothrombin time) remained normal throughout in all three cases, but all had proteinuria with red cells and tubular casts in the urine. Renal function was normal in all at follow-up one month later.

In overdosage paracetamol causes renal tubular necrosis in the same way that it damages the liver—that is, through the covalent binding of a highly reactive metabolite which is normally trapped by conjugation with reduced glutathione.[3] Thus sulphydryl compounds such as *N*-acetylcysteine prevent renal as well as hepatic damage after paracetamol overdosage if given within 10 hours.[4] The possibility of renal failure should always be kept in mind in patients who have not received adequate treatment for paracetamol poisoning. In our experience this complication is invariably heralded by back pain with proteinuria and haematuria within 36-48 hours of ingestion of the paracetamol.

L F PRESCOTT
A T PROUDFOOT
R J CREGEEN

Regional Poisoning Treatment Centre,
Royal Infirmary,
Edinburgh EH3 9YW

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Acetazolamide and symptomatic metabolic acidosis in mild renal failure

SIR,—Drs D N Maisey and R D Brown (5 December, p 1527) drew attention to acidosis caused by the acute introduction of acetazolamide in patients with renal impairment. We here report the occurrence of clinically significant hyperchloraemic acidosis in a diabetic woman on long-term treatment with the drug.

A 46-year-old insulin-dependent diabetic with proteinuria (1·6 g/day), but with normal urea and creatinine, had been treated for neovascular glaucoma with acetazolamide 500 mg twice daily for two years. She developed hyperglycaemic ketoacidosis as a result of septicaemic illness, having previously been well controlled on twice-daily isophane insulin. Following treatment with intravenous saline, insulin, and antibiotics, the ketoacidosis and hyperglycaemia resolved, but she remained clinically and biochemically severely acidotic. After three days the acetazolamide was withdrawn and she made a rapid recovery. When she was rechallenged with acetazolamide (500 mg twice daily) for five days asymptomatic acidosis recurred (table), and remained until the drug was stopped.

Although prolonged hyperchloraemic acidosis may follow diabetic ketoacidosis under other circumstances,[1] we believe that in this case it was caused by acetazolamide. This draws attention to the risk of acidosis in those who are on long-term treatment with the drug, even if they have a normal serum creatinine. As patients with diabetes mellitus are susceptible both to mild renal impairment and to metabolic acidosis, this risk should be borne in mind when acetazolamide is prescribed.

MARK GOODFIELD
JULIAN DAVIS
WILLIAM JEFFCOATE

City Hospital,
Nottingham NG5 1PD

[1] Oh MS, Banerji MA, Carroll HJ. *Diabetes* 1981;30:310-3.

Hyperchloraemic acidosis in diabetic woman treated with acetazolamide

(The ketoacidotic illness started on 2 November 1981; acetazolamide was discontinued on 5 November and reintroduced on 15 November.)

	Date	Cl^- (mmol/l)	pH	P_{CO_2} (kPa)	HCO_3^- (mmol/l)	Base excess (mmol/l)
Before ketoacidosis	16 Sept	116	—	—	16·0	—
After ketoacidosis:						
On acetazolamide	5 Nov	113	7·19	4·40	11·3	−13·7
Off acetazolamide	6 Nov	100	7·40	5·09	23·3	0·0
Acetazolamide challenge	20 Nov	106	7·29	4·23	15·1	−8·0

Conversion: SI to traditional units—Chloride, bicarbonate, and base excess: 1 mmol/l = 1 mEq/l. P_{CO_2}: 1kPa ≈ 7·5 mm Hg.

Failure with the new triphasic oral contraceptive Logynon

SIR,—The report by Mr R A Fay (2 January, p 17) about the new triphasic oral contraceptive Logynon is disturbing. I wish to draw attention to another aspect of this preparation—that of possible failure in the first course and the lack of instructions to the patient to use additional contraceptive precautions when starting Logynon.

An 18-year-old patient of mine, who had not previously used a contraceptive, started Logynon on the first day of menstruation, as recommended. This period lasted five days and was entirely normal. She completed a 21-day course without omitting any tablets and without having any gastrointestinal disturbance. This course was followed by amenorrhoea. When seen 10 days later she was found to have a normal-sized uterus and an equivocal result in the Gravindex pregnancy test. After a further 10 days she noted symptoms of pregnancy and was found to have uterine enlargement and was definitely positive in the Gravindex test. It seems most probable that this girl became pregnant during the first course of Logynon. I do not doubt that she took the course conscientiously.

I am concerned because when this triphasic preparation was first launched I understood that additional contraceptive precautions were not necessary when Logynon was started, if the course was started on the first day of the period. This would be consistent with the findings of suppression of mid-cycle gonadotrophins and oestradiol and late-cycle progesterone from the first treatment cycle. The instruction leaflet for patients does not advocate additional precautions unless the woman is changing from another oral contraceptive and starting on the fifth day of menstruation.

With monophasic contraceptives marketed by Schering, the need for additional precautions in the first 14 days after starting the pill is clearly stated in the instruction leaflet. If other similar instances of pill failure have been noted when the woman has been starting Logynon, perhaps the instruction leaflet should recommend additional contraceptive measures for the first two to three weeks.

HELEN GRAHAM

London SE22 0SQ

**We sent a copy of this letter to Dr Bye, of Schering Chemicals Limited, whose reply is included in the letter below.—ED, *BMJ*.

SIR,—The case report by Mr R A Fay (2 January, p 17) of a pregnancy in a user of Logynon is unremarkable, coming as it does 20 months after Schering's introduction of that highly successful oral contraceptive.

It is, of course, impossible to work out the "theoretical" efficacy of an oral contraceptive, since the investigator can never be sure what errors of administration have occurred, this being in the hands of the users. Moreover, even if in trials involving thousands of cycles administration could be independently verified, the limits of confidence for such rare events as pregnancies in trials of combined oral contraceptives are such that "theoretical" efficacy could never be accurately quantified.

What is of practical importance, however, is use effectiveness. Past experience shows that this varies widely from series to series because of the overwhelming effect of errors in the administration. Nevertheless, after a number of years of experience of the use of combined oral contraceptives by millions of women in different countries, a consensus of opinion was formed that the failure rate was of the order of 0·1 per 100 women-years. Clinical trials of Logynon, conducted before its introduction into Britain, gave no reason to assume that its efficacy was not of the same order.

Now, since the introduction of Logynon, over 3 million packs have been sold and, with sales of the same formulation by Wyeth, total sales since the introduction of the formulation have exceeded 5 million cycles. Even if we allow for the fact that some of these packs will not yet have been used, with a failure rate of 0·1 per 100 women-years well over 400 pregnancies would by now have been expected. It would be absurd to suggest that the case reported by Mr Fay and the seven reported to the Committee on the Safety of Medicines give any indication of the true total, but equally absurd to conclude that they are any cause for concern.

The same general observations apply to the pregnancy that Dr Graham reports. The probability of conception during one cycle of unprotected coitus has been estimated at about